IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICALS U.S.A., INC., Plaintiff, v. WEST-WARD PHARMACEUTICAL CORPORATION, HIKMA AMERICAS INC., and HIKMA PHARMACEUTICALS PLC, Defendants.	Civil Action No. 14-cv-1268 **REDACTED - PUBLIC VERSION**

DEFENDANTS' OPPOSITION TO TAKEDA'S MOTION FOR A PRELIMINARY INJUNCTION

PROCTOR HEYMAN LLP
Dominick T. Gattuso
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@proctorheyman.com

Attorneys for Defendants West-Ward Pharmaceutical Corporation, Hikma Americas Inc. and Hikma Pharmaceuticals PLC

DATED: October 17, 2014 - Original Filing Date
DATED: October 24, 2014 - Redacted - Public Version

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

INTRODUCTION

Takeda hopes to protect its branded colchicine product, Colcrys®, by seeking a preliminary injunction that would stop Defendants (collectively, "Hikma") from launching an authorized generic of their own branded product, Mitigare™. But no such injunction should issue for a simple reason: Hikma's competing product, approved by the Food and Drug Administration ("FDA") through the well-recognized § 505(b)(2) pathway, is labeled *solely* for a *non-infringing* use—a use that also is the most common, accounting for at least 95% of the colchicine market. Indeed, patented uses are affirmatively disclaimed and discouraged.

According to Takeda, an injunction is necessary because Hikma allegedly "will induce infringement" of Takeda's patents directed to the remaining 5%. (D.I. 1, ¶¶ 39, 46, 53, 60, 67.) But this Court already has found—and Takeda concedes—that Hikma's "label does *not* instruct users to perform the patented method[s.]" (D.I. 21, ¶¶ 1 (emphasis added), 4; Br. at 4.) This finding, alone, bars Takeda's claims as a matter of law. The full Federal Circuit has made clear that inducement requires "[e]vidence of *active steps* . . . taken to *encourage* direct infringement, such as advertising . . . or instruct[ions]." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006) (en banc in relevant part) (emphasis added). Takeda does not allege and cannot demonstrate any such "active steps taken to encourage" infringement, thus foreclosing Takeda's inducement claims and its request for a "drastic and extraordinary remedy." *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1324 (Fed. Cir. 2004). Mitigare™'s label *omits* instructions from the Colcrys® label, and *discourages* infringement with warnings and limitations.

Takeda's goal here is clear: it hopes to maintain monopoly prices by depriving consumers of a lower-priced, *non-infringing* colchicine product. But Takeda did not invent colchicine, an ancient drug that has been used for centuries as a prophylactic treatment for gout (a form of arthri-

tis). Instead, Takeda simply was the first to obtain formal FDA approval for this previously unregulated drug and, through its testing, obtained the five patents-in-suit. These patents, however, are directed to extremely limited methods of using colchicine: (1) in a lower dose to avoid potential toxicity in the extremely rare circumstance where it must be co-administered with one of three other drugs; and (2) to treat *acute* gout flare-ups, which occur infrequently when patients take colchicine as a prophylaxis to prevent their occurrence. Collectively, Takeda's patented methods comprise, *at most*, just 5% of all colchicine sales—and, again, with no such sales encouraged by Mitigare™'s label. Yet these peripheral patents have allowed Takeda to monopolize the entire market, causing the price for this very old drug to skyrocket from "~10 cents/pill to $5/pill" (Helfgott Decl. ¶ 31, Ex. K at 1[1]), resulting in "an extreme cost burden to patients who take colchicine for gout prophylaxis" (*id.*).

Hikma was one of many companies that sold colchicine tablets before FDA required all colchicine to go through formal approvals. Over the past few years, Hikma had been working closely with FDA to obtain approval of its own colchicine product that could compete with Colcrys® for use as prophylaxis therapy—the 95% *non-patented* market segment. With FDA's guidance, Hikma pursued the New Drug Application ("NDA") pathway under § 505(b)(2) of the Hatch-Waxman Act, which allows applicants to seek approval of a drug that differs from a previously approved drug product. Applications under § 505(b)(2)—the pathway Takeda itself used to develop Colcrys®—require more testing than an Abbreviated New Drug Application ("ANDA") and are thus more expensive. And, because Hikma's 505(b)(2) product is a "new" drug (as opposed to a duplicate, ANDA generic of Colcrys®), it is not therapeutically equivalent, contains a different label, is in a capsule (as opposed to the Colcrys® tablet) formulation, and *will not* be automatically

[1] Unless otherwise indicated, all Exhibits are attached to the Declaration of Dominick Gattuso.

substituted at pharmacies for Colcrys®. Hikma's product will instead compete with Colcrys® based on its own merit and price. (This regulatory process is discussed in more depth in the Hansten, Tsien and Todd Declarations.)

Without the benefit of full briefing, the Court noted its initial "impression that Hikma has effectively side-stepped the ANDA regime" by not providing Takeda a Paragraph IV certification. (D.I. 21, ¶ 8.) But Takeda has given the Court the wrong impression. Mitigare™ is not a generic of Colcrys®. Hikma's application did not even rely on Colcrys® as a listed drug. Instead, Hikma referred to a different, unpatented colchicine formulation—the same formulation Takeda itself relied on to obtain FDA approval for the Colcrys® prophylaxis indication. Because Hikma did not rely on any of Takeda's data, nor seek approval for its patented methods, Takeda had no statutory right to receive notice of Hikma's confidential application. This situation is hardly unique. As the Federal Circuit explained in the analogous section viii context, "a [Paragraph IV] certification *need not be provided* for a patent claiming a use for which the ANDA applicant is not seeking approval[.]" *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1361 (Fed. Cir. 2003) (emphasis added). That was the situation here, where Hikma did not seek approval for any patented indication. FDA agreed, finding Hikma's proposed regulatory pathway to be reasonable. (Gattuso Decl. ¶6 Ex. D). In fact, FDA is currently defending the regulatory process chosen by Hikma—including FDA's position that no Paragraph IV certification was required—before the U.S. District Court for the District of Columbia. (*Id.*).

Takeda has succeeded in obtaining a temporary injunction under expedited circumstances without the benefit of full briefing, but it cannot meet the preliminary injunction requirements for at least the following reasons:

Takeda Cannot Show Any Likelihood Of Proving Induced Infringement. Prompted by

Takeda's pleas to maintain a temporary status quo and request for a rushed ruling, the Court found that Takeda was likely to succeed on the merits based on the preliminary filings. In doing so, the Court distinguished Federal Circuit cases that bar inducement liability where "proposed labeling explicitly and undisputedly carve out all patented indications"—no matter the "market realities." *AstraZeneca Pharm. LP v. Apotex Corp.*, 669 F.3d 1370, 1380 (Fed. Cir. 2012) ["*AstraZeneca 2012*"]. As the Court explained: "Because the infringement analysis need not reflect the artificial construct of ANDA litigation, [the Court is] not confined to the principle that 'section 271(e)(2)(A) lies only against a patented use that has been approved by the FDA[.]'" (D.I. 21, ¶ 3.)

But even outside the limited construct of ANDA litigation, inducement liability still requires "[e]vidence of *active steps* . . . taken to *encourage* direct infringement." *DSU*, 471 F.3d at 1305 (emphasis added). The Federal Circuit has made this point clear, conclusively shutting the door on Takeda's inducement claim: "If an off-patent drug is being used for an unpatented use, that is activity *beyond the scope of § 271(a)*"—that is, beyond the Patent Act as a whole. *AstraZeneca 2012*, 669 F.3d at 1380 (emphasis added).

We thus respectfully ask the Court to revisit its TRO analysis, particularly because it will have what we believe is an unintended industry-wide impact—nullifying Congressionally approved pathways for generic drug approval under the Hatch-Waxman Act. As the Supreme Court has explained in a similar context, an applicant may carve out "from the brand's approved label the still-patented methods of use"—either through a 505(b)(2) application (as here), or through a "section viii statement" (in the ANDA context). *Caraco Pharm. Labs v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1676-77 (2012) (internal quotation marks omitted). Even where an ANDA applicant copies the branded drug, "FDA acceptance of the carve-out label allows the generic company to place its drug on the market (assuming the [application] meets other requirements), but only for a

subset of approved uses—i.e., those not covered by the brand's patents." *Id.* at 1677.

The Court's TRO ruling, however, effectively forecloses this "carve out." Here is why. It is undisputed that Hikma did not seek (or obtain) FDA approval for a patented use. Instead, it "will market the drug for one or more methods of use not covered by the brand's patents." *Id.*. As this Court correctly found, "in its proposed label, Hikma has omitted specific mention of uses for which Takeda has patent protection" (D.I. 21, ¶ 1)—that is, Hikma's "Mitigare™ label does not *instruct* users to perform the patented method" (D.I. 21, ¶ 4).

Instead of relying on the instructions in Hikma's label, the TRO stopped Hikma's launch based solely on Hikma's purported *knowledge* given "the realities of the marketplace in which the parties compete"—namely, that some doctors may prescribe Hikma's drug for "*off-label*" infringing uses (i.e., uses omitted from Hikma's label). (D.I. 21, ¶ 3 (emphasis added).) But even assuming Hikma had that "knowledge," it is legally insufficient to support a finding of induced infringement. "[I]nducement requires evidence of *culpable conduct*"—that is, "active steps"—"directed to encouraging another's infringement, *not merely that the inducer had knowledge of the direct infringer's activities*. *DSU*, 471 F.3d at 1305-06 (emphasis added).

If mere "knowledge" of off-label prescribing *were* enough to demonstrate induced infringement—contrary to Congressional intent—generics could no longer enter the market by carving out patented uses from their labels. Given "the realities of the marketplace" (D.I. 21, ¶ 3), market participants (generics and brands alike) *always* know that, despite strict adherence to on-label marketing as required by law, doctors might prescribe, in their sole and absolute medical discretion, drugs for uses that do not appear on a generic company's label. So mere general knowledge that doctors sometimes engage in off-label prescribing would mean even patents covering minor drug uses that do not appear on the generic label (like here, where the patented uses are directed to less

than 5% of the market), would give brand companies an unintended monopoly over the entire market (like here, where Takeda's patents do not cover at least 95% of colchicine sales). This is not the law.

In short, as explained in more depth in the Helfgott, Gall, Silverman and Saseen Declarations, Takeda's failure to show "active steps to encourage" infringement means it has no likelihood, much less a reasonable likelihood, of successfully proving infringement.

Hikma Raises Substantial Questions Of Invalidity. Independent of Takeda's weak infringement claim, no preliminary injunction should issue because Hikma is raising "substantial question[s] concerning . . . validity." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343,1350-51 (Fed. Cir. 2001). For example, Takeda's two patents covering treatment of an acute gout flare with a specific dose are anticipated, or at least obvious, because the option of using that exact dose was already known—and practiced—before the patents were filed. Takeda's remaining three patents covering co-administration of colchicine with three particular drugs at reduced doses also are obvious, because they merely claim routine dose adjustments. "[I]t is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012).

Any Harm Would Be* De Minimis, *Not Irreparable. Nor has Takeda met its heavy burden of showing irreparable harm. Takeda argues it would be irreparably harmed by generic competition as a whole. To show irreparable harm, however, the Federal Circuit requires "that a sufficiently strong causal nexus relates the alleged harm to the alleged infringement." *Apple, Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012) ["*Apple II*"]. Takeda ignores—and, more importantly, has made no effort to satisfy—this nexus requirement. It cannot show any such "nexus"—much less a "strong" one—between its alleged harm (competition as a whole in a market

where 95% of sales are non-infringing), and "the alleged infringement" (which, at the very most, is *de minimis* direct infringement, assuming the patents are even valid). (D.I. 6 at 8-10, 12-14.)

Should Takeda ultimately prevail in showing induced infringement (which it cannot), infringement of less than 5% of the market can be addressed with damages. There is no need for an injunction covering 100% of the market.

The Balance Of Hardships And Public Interest Cut Against An Injunction. A preliminary injunction would cause significant, irreparable and competitive hardship to Hikma—which has invested [redacted] to launch what would have been the only competing single-ingredient colchicine product in a $600 million market, [redacted]. The TRO is [redacted] And, as explained in the Gavaris and Snail declarations, extending the TRO would *invert* the status quo, [redacted].

Finally, the public interest also cuts against injunctive relief. Absent an injunction, patients stand to benefit from price competition in a market that is almost entirely *not patented*—and where Takeda's limited and weak patents have allowed it to charge monopoly prices for the entire market. As the American College of Rheumatology explained, Takeda's monopoly has allowed it to take a substantial price hike, which has "creat[ed] new financial hardship for . . . patients" (Helfgott Decl. ¶ 31, Ex. K. at 2.) so that Takeda could rake-in in about $600 million a year. Takeda has achieved and exhausted regulatory exclusivity for its pertinent colchicine testing, so the time is right for lawful competition that benefits consumers.

BACKGROUND

History of Colchicine. This case involves the ancient drug colchicine, which is derived

from plants and has been known to treat gout (a form of arthritis) since about the sixth century. Ex. 1 at 2045-46. Colchicine has been sold to treat gout in the United States since the nineteenth century, before the FDA even existed. *Id.* And because it had been in use for so long, from the nineteenth century until about 2010, companies were selling colchicine drug products without needing FDA approval. *Id.*

In the 1960s, FDA approved the new drug ColBenemid, a fixed-dose combination product of probenecid and colchicine based on FDA's determination that this product was safe. (Ex. 2, Letter from J. Woodcock to G. Veron, FDA Docket No. FDA-2010-P-0614 (May 25, 2011), at 4.) Shortly thereafter, FDA began approving drugs only if proven safe and effective, so the FDA initiated the Drug Efficacy Study Implementation ("DESI") review to evaluate the effectiveness of drugs previously approved on safety grounds only. (*Id.*) The DESI review demonstrated that ColBenemid was effective for the treatment of chronic gouty arthritis. (*Id.*) In 1976, the FDA approved Col-Probenecid, another fixed-dose combination product of probenecid and colchicine, based on the safety data for ColBenemid and the effectiveness finding from the DESI review. *Id.*

Hikma's Colchicine Product Development. Hikma had been legally selling colchicine since at least 1972, until it was temporarily ordered off the market in 2010 by the FDA so that FDA could undertake a review of the colchicine market. Hikma has been working with FDA since to further develop and re-launch the product. While other generic applicants chose the ANDA pathway, Hikma chose a different option—the § 505(b)(2) New Drug Application (NDA), discussed in the Tsien Declaration. At first, with FDA's consent, Hikma filed a § 505(b)(2) application to launch a colchicine *tablet* (like Colcrys®) that relied on longstanding literature, not Takeda's studies, to support a prophylaxis indication. But Hikma had to withdraw that application

in response to an FDA citizen petition filed by Takeda's predecessor, Mutual Pharmaceutical Company. In its ruling, FDA found that Hikma had to file an ANDA for a *tablet* formulation constituting a Colcrys® "duplicate." (D.I. 9, Ex. J at 12.)

In this same ruling, however, FDA put Takeda on notice that Hikma—or, for that matter, any other generic drug manufacturer—could use the 505(b)(2) pathway to develop a non-"duplicate" colchicine product, such as a *capsule*. In particular, "FDA denie[d] Mutual's request that any 505(b)(2) application for a single-ingredient oral colchicine product must necessarily cite Colcrys as its listed drug," which would have required a Paragraph IV certification. (*Id.* at 3.) FDA explained that its review of "another 505(b)(2) application for a single-ingredient colchicine product that does not cite Colcrys as a listed drug . . . will depend on the facts and circumstances of the particular application and a blanket refusal to review any such application is not warranted at this time." (*Id.* at 21.)

Hikma thus continued to work with FDA to further develop a non-infringing colchicine product that did not reference Colcrys®. After meetings and discussions with FDA, Hikma filed a new 505(b)(2) application to approve its own branded Mitigare™ colchicine product in the form of a *capsule*. Hikma did not reference Takeda's Colcrys® *tablet* product and was under no obligation to do so. Instead, like Takeda, Hikma's application relied on its own testing and referenced Col-Probenecid, the old colchicine/probenecid combination product discussed above. Nor did Hikma have any obligation under the Hatch-Waxman Act or any statute or regulation to provide Takeda with a Paragraph IV certification. (*See* Tsien Decl., ¶¶ 28-34, 40) FDA, which is charged by Congress to administer the FDC Act and the Hatch-Waxman Act, agreed (and is defending this position in related litigation). (Gattuso Decl. ¶ 6, Ex. D at 18-19.)

On September 26, 2014, after years of intense review, FDA approved Hikma's application

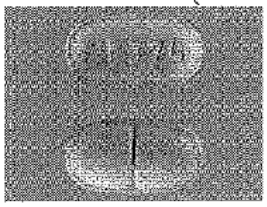
for a centuries-old, publicly-known indication, i.e., using colchicine for prophylaxis of gout flares. (D.I. 9, Ex. A at 1.) To be clear, there was no "side-stepp[ing]" or gaming of the statutory drug-approval pathways. (D.I. 21, ¶ 8.) Indeed, this case is different than the situation the Court addressed last month, where Par Pharmaceutical amended its ANDA to carve out the gout indication from its label and seek approval for "the nominal FMF market." *Takeda Pharms. U.S.A., Inc. v. Par Pharm. Co.*, 2014 WL 4402965, at *5 (Sept. 4, 2014). Hikma, in essence, has merely obtained FDA approval to reenter the market in which it had already been participating for years before Colcrys® ever became available. And, again, Hikma's product is approved for the most common—and non-patented—prophylaxis indication, constituting at least 95% of the market. (Helfgott Decl. ¶ 31; Gall Decl. ¶ 6)

On October 3, one week after it obtained FDA approval, Hikma fully launched its branded Mitigare™ product and pursued its plan to have a less-expensive, authorized generic of Mitigare™ (not a generic of Colcrys®) ready for dispensing by pharmacies within a week later. That same day—again, a week after FDA approval—Takeda filed suit. On October 9, almost two weeks after FDA approval, the TRO halted Hikma's generic launch.

Takeda's Narrow Patents. Takeda is asserting five patents covering two types of limited uses. The "Co-Administration Patents"—U.S. Patent Nos. 8,097,655; 7,964,648; and 8,440,722—address a tiny market segment (less than 1%), where colchicine must be co-administered in specific reduced doses (mostly 0.3 mg) with three other drugs (clarithromycin, ketoconazole and verapamil). The "Acute Gout Flare Patents"—U.S. Patent Nos. 7,964,647 and 7,981,938—claim methods of treating acute gout flares (not prophylaxis) through administration of 1.2 mg (2 pills) followed by 0.6 mg (1 pill) an hour later.

Product Comparison. To be clear, Mitigare™ (or its generic) is not a generic of Colcrys®.

The two products have material differences summarized in the following table:

	Colcrys®	Mitigare™
Dosage Form	Scored Tablet (0.6 mg) 	Capsule (0.6 mg) 
Indication(s) (maximum dose)	1. Acute Gout Flare (*1.8 mg*) 2. Prophylaxis (.6 or 1.2 mg) 3. Familial Mediterranean Fever (2.4 mg)	1. Prophylaxis (.6 or *1.2 mg*)
Co-administration warning	Reduce dose to *0.3 mg* (0.6 mg can be used only with 240 mg verapamil)	"[S]hould be avoided," but if "necessary" reduce dose
Is 0.3 mg dose possible?	Yes, split tablet	Splitting "not feasible"

ARGUMENT

Injunctive relief is an "extraordinary remedy" granted only in "limited circumstances." (D.I. 21, ¶ 2 (citations omitted)). This case is not one of them.

I. Takeda Has Failed To Show Likelihood Of Success On The Merits.

Hikma's substantial non-infringement and invalidity defenses are discussed below.

A. Takeda Has No Reasonable Likelihood Of Showing Induced Infringement.

For the reasons demonstrated below, Takeda's claims for induced infringement under 35 U.S.C. § 271(b) all fail as a matter of law. (Gattuso Decl. Ex. C, Noninfringement Chart.)

1. Takeda Cannot Prove Inducement, Because It Concedes Hikma Has Taken No Active Steps To Encourage Infringement.

Takeda concedes Hikma cannot *directly* infringe its patents, because Hikma is a manufacturer who does not administer drugs. Instead, Takeda's claims are based solely on an *indirect* theory of inducement. This means it must show "specific intent to encourage another's infringement"—a showing that can be made only with "[e]vidence of *active steps*" . . taken to *encourage* direct infringement, such as advertising . . . or instruct[ions]." *AstraZeneca LP v. Apotex, Inc.*,

633 F.3d 1042, 1056 (Fed. Cir. 2010) ["*AstraZeneca 2010*"] (quoting *DSU*, 471 F.3d at 1306 and *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005)) (emphasis added).

Takeda's allegations of induced infringement are directed solely to the Mitigare™ label. Where, as here, inducement is based solely on a product's labeling (*see* D.I. 1 ¶¶ 33-36), "[t]he pertinent question is whether the proposed label *instructs* users to perform the patented method." *AstraZeneca 2010*, 633 F.3d at 1060 (emphasis added). The Court already answered this precise question in the negative, finding that "the Mitigare™ label does *not instruct* users to perform the patented method[.]" (D.I. 21, ¶¶ 1, 4 (emphasis added); *see also* Br. 4).)

Even in the context of ANDA generics, where the market reality is that drugs are bioequivalent and automatically substituted, the Federal Circuit made it clear that there is no induced infringement if "the label, taken in its entirety, fails to recommend or suggest to a physician that [the pharmaceutical product] is safe and effective for inducing the claimed combination of effects in patients in need thereof." *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1322 (Fed. Cir. 2012). The Court of Appeals found particularly "unpersuasive," and "contrary to the [Hatch-Waxman] statutory scheme," the argument Takeda makes here—that "restricted generic labeling ignore market realities because even if a generic drug is formally approved only for unpatented use[s], pharmacists and doctors will nonetheless substitute the generic for all indications once it becomes available." *AstraZeneca 2012*, 669 F.3d at 1380.

Here, the facts are substantially stronger. Mitigare™ is not Colcry®'s generic—the products are not bioequivalent and they *cannot* be automatically substituted at the pharmacy. (Saseen Decl. ¶ 17.) Because the two products have very different labels, it is even more important to enforce the inducement requirement of "active steps" that encourage infringement. *DSU*, 471 F.3d at 1305. Both in and out of the Hatch-Waxman framework, and regardless of the industry, this

"active steps" element requires more than "knowledge that [the product] may be put to infringing uses." It requires "statements or actions directed to promoting infringement[.]" *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1341 (Fed. Cir. 2008) (per curiam).[2]

Because Hikma's label admittedly "omitted specific mention of uses for which Takeda has patent protection (Br. at 5), to sustain its § 271(b) inducement claim, Takeda needs to point to other evidence of "active steps . . . taken to encourage direct infringement[.]" *AstraZeneca 2010*, 633 F.3d at 1059 (citations and internal quotation marks omitted). But Takeda has not alleged or even attempted to demonstrate such active steps—instead, the inducement allegations rely *solely* on Hikma's labeling, which is legally and factually insufficient. (D.I. 1, ¶¶ 33-36.) In the absence of any "active steps" by Hikma to encourage infringement, Hatch-Waxman cases like *Warner–Lambert*, *Bayer* and *AstraZeneca 2012* finding no inducement liability as a matter of law apply equally here.

Indeed, Takeda's argument turns controlling precedent on its head. According to Takeda, "Hikma's label *makes no effort to stop doctors and patients from using its 0.6 mg colchicine product [off-label] in an infringing manner*." Br. 14 (emphasis added). But of course, that is not the standard. Notwithstanding the fact that this statement is incorrect given the label's limitations and warnings (Gattuso Decl. ¶3, Ex. A; Helfgott Decl ¶ 28-30), the "pertinent question" is *not* whether the label expressly discourages or bars infringement—it is "whether the proposed label instructs users to perform the patented method." *AstraZeneca 2010*, 633 F.3d at 1060. The answer is no.

---

[2] *See also AstraZeneca 2010*, 633 F.3d at 1059 (holding that, as here, "where a product has substantial noninfringing uses, *intent to induce infringement cannot be inferred* even when the [alleged inducer] has *actual knowledge* that some users of its product may be infringing the patent" (alteration in original) (emphasis added)); *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1276 n.6 (Fed. Cir. 2004) (holding that "sale of a lawful product by lawful means, with the knowledge that an unaffiliated, third party may infringe, cannot, in and of itself, constitute inducement of infringement" (internal quotation marks omitted)).

(Br. 4.)

2. Takeda Failed To Show Direct, Much Less Induced, Infringement Of The Co-Administration Patents.

In an effort to avoid the case-dispositive precedent discussed above, Takeda argues that Hikma's label would "inevitably lead some customers to practice the claimed method" in the Co-Administration Patents. (D.I. Br. 11 (quoting *AstraZeneca 2010*, 633 F.3d at 1060).) This is false. In fact, there is no evidence of direct, much less induced, infringement.

a. Takeda Has Failed To Show *Direct* Infringement.

"[I]nducement liability may arise if, but only if, [there is] . . . direct infringement." *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S. Ct. 2111, 2117 (2014). Takeda cannot even make the predicate showing of direct infringement here.

The Court found that "prescribing and filling prescriptions (by doctors and pharmacists) and use (by patients) of Mitigare™ for prophylaxis of gout flares will *directly* infringe representative claims of the '655, '648, and '722 patents[.]" (D.I. 21, ¶ 6 (emphasis added).) But any such direct infringement based on "off-label prescribing" (*id.* ¶ 4) would be highly speculative.

To be clear, the Co-Administration Patents cover less than 1% of the colchicine market. (Helfgott Decl ¶ 38; Hansten Decl. ¶¶15, 16; Gall Decl. ¶ 7.) Indeed, none of these patents claim a method for prophylaxis of gout flares *unless* there is *both*:

1. A "*concomitant administration*" of colchicine with specific drugs (clarithromycin, ketoconazole, and verapamil), *and*

2. *The colchicine dose is reduced* from the typical 0.6 mg dose taken once or twice a day to a lower dose within specifically claimed ranges (typically 0.3 mg).

(Br. 5; D.I. 9, Exs. M, O, and P (emphasis added).) It is highly unlikely that *any* doctor or patient will use Mitigare™ according to these claim limitations for three independent reasons:

First, it is not even physically possible for doctors to prescribe Mitigare™ capsules in a

manner that infringes the specific dosing claimed by the '655 and '648 patents. Takeda admits that these patents require a reduced colchicine dose of "*0.3 mg* once per day." (Br. 7, 9 (emphasis added); D.I. 6 Br. at 13.) But Mitigare™ does not come in a 0.3 mg dose—it is a *0.6 mg* capsule. Takeda concedes that "[b]ecause Mitigare™ is a capsule"—unlike Colcrys®, a tablet—"splitting the dose" to obtain a 0.3 mg dose "is not feasible." (D.I. 7, ¶ 18; *see also* Saseen Decl. ¶ 14.)

Second, while direct infringement of the '722 patent at least theoretically is possible, the patented claims require that this would occur only in the extremely unlikely event a doctor prescribes Hikma's colchicine product with 240 ml verapamil, despite (1) the existence of several alternative therapies for verapamil, and (2) the fact that verapamil is administered in a large variety of doses (the 240 ml verapamil is *not* suggested in the Colcrys® labeling). (Helfgott Decl ¶ 42.) The chance of this happening is slim to none. (Hansten Decl. ¶ 15, 16; Gall Decl. ¶ 7; Silverman Decl. ¶ 9.)

Third, Mitigare™'s product label expressly warns that "[c]oncomitant use" of Mitigare™ with these drugs "should be avoided if possible." (Helfgott Decl. 28¶_Ex. J.) There are myriad alternatives for ketoconazole, clarithromycin, and verapamil such that it is highly unlikely any doctor or patient would find it necessary to coadminister them with colchicine, rendering any direct infringement highly speculative. (Helfgott Decl. ¶ 29; Hansten Decl. ¶ 15; Gall Decl. ¶ 7; Silverman Decl. ¶ 9.)

b. Even Assuming Direct Infringement, There Is No *Inducement.*

Even assuming some hypothetical, *de minimis* direct infringement, Takeda could not hold Hikma liable for inducement for four reasons. First, Takeda concedes that Mitigare™'s label "does not provide any directions" for infringing uses. (D.I. 6 Br. 13) Takeda improperly broadens the scope of inducement liability by arguing that this *lack of information* would lead some doctors, on their own, to look to third-party materials for guidance on non-labeled uses. (D.I.6 Br. at 13.)

Again, his flawed theory cannot be squared with the "active steps" requirement mandated by law to prove inducement. *DSU*, 471 F.3d at 1305.

Second, far from constituting an active step encouraging infringement, Hikma's label—"taken in its entirety," *Bayer*, 676 F.3d at 1324, warns doctors that the claimed co-administration therapy "*should be avoided.*" (Helfgott Decl. ¶ 28, Ex. J.) This warning not only makes direct infringement speculative, it makes inducement impossible. The label hardly "recommend[s] or suggest[s] to a physician that [the product] is safe and effective for inducing the claimed combination of effects in patients in need thereof." *Bayer*, 676 F.3d at 1324; *United Therapeutics Corp. v. Sandoz*, 2014 WL 4259153, at *18 (D.N.J. 2014) (no intent inferred based on "warning," which differs from "instruction"). And "[h]ypothetical instances of direct infringement are insufficient to establish vicarious liability or indirect infringement." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1313 (Fed. Cir. 2007).

This case is thus distinguishable from *AstraZeneca 2010*, cited by Takeda, where the drug's label expressly said the infringing use was "*desirable*" and, thus, the Federal Circuit found such language "would inevitably lead some consumers to practice the claimed method. 633 F.3d at 1057, 1060 (emphasis added). Here, the patented uses are not even remotely desirable. Again, Hikma's label says the claimed methods "should be avoided if possible," thus *dis*couraging doctors to use this method and find non-infringing alternatives. (Helfgott Decl. ¶ 28 Ex. J.)

Third, Hikma has no inducement liability because where, as here, "a product has substantial non-infringing uses, *intent to induce infringement cannot be inferred* even when the [alleged inducer] has *actual knowledge* that some users of its product may be infringing the patent." *AstraZeneca 2010*, 633 F.3d at 1056, 1059 (emphasis added); *see also ACCO* , 501 F.3d at 1313-14 (holding that "[t]he mere sale of a product capable of substantial non-infringing uses does not

constitute indirect infringement of a patent"). Takeda cannot credibly dispute that Hikma's product indicated for 95% of the market has substantial non-infringing uses.

Fourth, Takeda's inducement theory is foreclosed under the analogous doctrine of "[p]rosecution history estoppel," which "requires that the claims of a patent be interpreted in light of the proceedings in the PTO during the application process." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 733 (2002). During prosecution, the examiner repeatedly rejected the claims in the Co-Administration Patents as obvious based on prior art saying virtually the same thing as Hikma's label.[3] Takeda overcame this rejection by arguing that this this prior art—again, the same language from Hikma's label—is insufficient to lead to the patented dose reductions, because "*no specific dose reduction is recommended.*" (Gattuso Decl. ¶ 8 Ex. F at 4 (emphasis added)). Takeda would have this Court find the opposite.

3. Takeda Failed To Show Induced Infringement Of The Acute Gout Flares Patents.

There also can be no inducement of the Acute Gout Flares Patents because, as Takeda concedes, "Hikma's label does not provide any directions for the treatment of acute gout flares." (Br. at 13.) Indeed, the Mitigare™ label makes it clear in the first section, addressing "INDICATIONS AND USAGE," that Mitigare™ should *not* be used for acute gout flares treatment:

> *Limitations of use*:
>
> The safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied.

(D.I. 9, Ex. B at 1 (emphasis added).) This undisputed fact, alone, forecloses infringement liability.

---

[3] (*Compare* Helfgott Decl. ¶ 50 (prior art: "it would be prudent to avoid [the types of drugs at issue] with colchicine," but "[i]f it is absolutely necessary to use [these drugs] with colchicine, consider decreasing the colchicine dose. . . ."), *with* Helfgott Decl. ¶ 28, Ex. J (Mitigare™ label: "Concomitant use of MITIGARE™ and [the types of drugs at issue] should be avoided if possible. If co-administration of" these drugs "is necessary, the dose of MITIGARE™ should be reduced . . .").

Instead of encouraging infringement, Hikma "limit[s]" its use for a patented indication. The label cannot induce infringement unless it "recommends or suggests to physicians that the drug is safe and effective for" the patented method. *Bayer*, 676 F.3d at 1322.

In the TRO ruling, the Court found that "the record indicates that it is likely that some patients may use the same medication they use for prophylaxis to treat an acute gout flare when it occurs, *because the dosing is similar* (administration of '0.6 mg (one capsule) once or twice daily')." (D.I. 21 ¶ 7 (emphasis added).) But this finding was in error. There is no dispute that dosing for the prophylaxis and acute gout flare indications is materially different.

As discussed above, the Mitigare™ label says: "The *maximum* dose is *1.2 mg per day.*" (*Id.* (emphasis added).) In contrast, the dosing for acute flares is "1.2 mg (two tablets) at the first sign of the flare followed by 0.6 mg (one tablet) one hour later"—a total of *1.8 mg in one hour*, at least 50% higher than the maximum *daily* dose approved by the FDA for Mitigare™. (D.I. 9, Ex. E at 3.) Thus Hikma's label explicitly suggests that its product should not be used for treatment of flares. This is why the Mitigare™ Medication Guide says: "If you have a gout flare while taking Mitigare™, tell your healthcare provider." (Helfgott Decl. ¶ 28, Ex. J)

The Court also suggested, at Takeda's urging, that there is a "limited market for Mitigare's approved use – prophylaxis only," because "the vast majority of gout patients using colchicine for prophylaxis also suffer acute gout flares." (D.I. 21, ¶ 7 (citing D.I. 7, ¶ 13) (emphasis added).) But Takeda offered no evidence that prophylaxis use is a "limited market," because such a statement would not be true. As explained in the Declarations of Drs. Helfgott and Gall, colchicine is *not* the drug of choice for patients suffering from acute gout flare. This is confirmed by the fact that prescriptions for the non-patented prophylaxis use account for about *95%* of the market. (Helfgott Decl. ¶ 31; Gall Decl. ¶¶ 4,5.) Takeda's argument also conflicts with what the American

College of Rheumatology told the FDA: "Rheumatologists *rarely use colchicine for acute gout flares* but utilize colchicine frequently for chronic gout prophylaxis." (Ex. – at 2 (emphasis added).)

B. Hikma Has Raised Substantial Questions Of Invalidity.

Independently of Takeda's meritless infringement claims, "[a] preliminary injunction should not issue" if Hikma "raises a substantial question regarding *either* infringement *or* validity." *AstraZeneca 2010*, 633 F.3d at 1050 (emphasis added). Hikma's invalidity arguments show "it is more likely than not" to succeed at trial, which is all it must show to defeat Takeda's motion. *Titon Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1379 (Fed. Cir. 2009). In fact, Hikma raises three substantial questions of invalidity, discussed below. (Gattuso Decl. Ex. C., Invalidity Chart)

1. The Acute Gout Flare Patents Are Anticipated Because They Were Practiced By Others In This Country Before They Were Patented.

The first substantial question of invalidity is whether the Acute Gout Flare Patents are invalid, because "*the invention was known or used by others in this country* . . . before the invention thereof by the application for patent"? 35 U.S.C. 102(a) (emphasis added). The answer is yes. Drs. Helfgott, Gall, and Silverman declare that they practiced the claimed dose, 1.2 mg of colchicine at the onset of an acute gout flare followed by 0.6 mg of colchicine an hour later, before the earliest priority date. (Helfgott Decl. ¶¶ 13, 46; Gall Decl. ¶ 5; Silverman Decl. ¶ 13.)

2. The Acute Gout Flare Patents Are Anticipated And/Or Obvious.

The second substantial question of invalidity is whether the prior art renders the Acute Gout Flare Patents anticipated, or at least obvious? The answer is yes. A prior art reference anticipates a claim "if it includes all of the elements and limitations of the claims and enables one of skill in the field of invention to make and use the claimed invention." *Merck & Co. v. Teva Pharma*

USA, Inc., 347 F.3d 1367, 1372 (Fed. Cir. 2003).

As explained in the Helfgott Declaration, the prior-art Leikin reference anticipates all claims of the Acute Gout Flare Patents by disclosing the claimed dosing—namely, 1.2 mg at the onset of the flare and 0.6 mg an hour later. (Helfgott Decl. ¶ 49 Ex. S) Leikin expressly teaches the following recommended dosing regimen for treating gout with colchicine: "Acute attacks: Oral: *Initial 0.6-1.2 mg, followed by 0.6 every 1-2 hours*; some clinicians recommend a maximum of 3 doses." (*Id.*) This reference discloses, at most, only *eight* specific treatment options—including the claimed dosing regime. (*Id.*) This disclosure is sufficient to anticipate, because it is "of such a defined and limited class that one of ordinary skill in the art could at once envisage each member of the genus." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC,* 683 F.3d 1356, 1361 (Fed. Cir. 2012). Even if not anticipated, the claimed treatment regimen would have been obvious because, as explained in the Helfgott Declaration (paragraphs 46-49), the claimed invention "merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citation omitted).

3. The Co-Administration Patents Are Obvious.

The third substantial question of invalidity is whether Takeda's Co-Administration Patents are invalid, because they merely claim *routinely-optimized dosing*? Once again, the answer is yes. The Co-Administration Patents are directed to using colchicine as follows:

Patent	Coadministered drug	% Reduction in Colchicine Dosage
'655	Clarithromycin	75% reduction
'648	Ketoconazole	50-75% reduction
'722	Verapamil	25-50% reduction

(Helfgott Decl. ¶ 43.) These reductions were hardly novel. As prior art, a *New England Journal of Medicine* reference taught that colchicine was "frequently used as prophylaxis against recurrent acute gout." (*Id.* ¶ 50, Ex. R at 1649). And the "*standard practice*" was "to use low-dose oral colchicine," i.e., "*0.6 mg orally twice a day.*" (*Id.*) As early as 1993, practitioners knew to use colchicine "in low dosage (0.6 to 1.2 mg/day) for prophylaxis of recurrent attacks of gout." Star, *Prevention and Management of Gout*, Drug 45(2) 112-222 (1993). With this foundation, the prior art encouraged a person of ordinary skill in the art to reduce doses of colchicine when concomitantly administered with the three other drugs at issue. (*Id.* ¶ 50.)

For example, the Horn & Hansten prior art reference taught that "colchicine can be very effective in the treatment of gout," but that because of drug toxicities, "[i]f it is absolutely necessary to use a PGP inhibitor [such as clarithromycin, ketoconazole and verapamil] with colchicine, consider *decreasing the colchicine dose*" and monitoring the patient. (Helfgott Decl., ¶ 50, Ex. U.) The Leikin reference recommended a *specific 50% dosage reduction.* (*Id.* ¶ 49, Ex. S.)

As explained in more depth in the Helfgott Declaration, it would have been obvious to one of ordinary skill in the art to follow the instructions of this and similar prior art, along with that person's own knowledge of drug interactions, to reduce colchicine doses—and to determine whether to give ¼, ½ or ¾ dose—when co-administered with other drugs that blocked colchicine's elimination in the body. *See In re Applied Materials*, 692 F.3d at 1295 ("it is not inventive to discover the optimum or workable ranges by routine experimentation").

In fact, Takeda cannot argue that the specific percentage of the reductions—25%, 50%, and 75%—are somehow novel or the result of a novel investigation. First, Takeda is essentially conceding its patents are invalid to the extent it argues that the Mitigare™ label—which, again, mirrors the prior art—is sufficient to lead one skilled in the art to the claimed, reduced doses. *See*

Schering Corp. v. Geneva Pharms., 339 F.3d 1373, 1379 (2003) (holding "that which would literally infringe if later in time anticipates if earlier"). Second, the inventor of the patents, Dr. Davis, merely conducted routine clinical trials with well-known and standard protocols to measure the drug-drug interactions to determine an appropriate dose reduction of colchicine. (Silverman Decl. ¶ 14; Helfgott Decl. ¶ 56). Indeed, Takeda admitted during prosecution of U.S. App. No. 13/092,459 (now U.S. Patent No. 8,093,297), that "the single dose study performed by Dr. Davis is the *standard study* in the art for drug approval." (Gattuso Decl. ¶ 9 Ex. H at 5 (emphasis added).) Takeda has no right to a patent, and monopoly prices, based on standard dose optimization.

II. Takeda Has Failed To Show Irreparable Harm.

No injunction should issue for an additional reason: Takeda has failed to show irreparable injury caused by Hikma's alleged induced infringement. "[T]o satisfy the irreparable harm factor in a patent infringement suit, a patentee must establish both of the following requirements: 1) that absent an injunction, it will suffer irreparable harm, and 2) *that a sufficiently strong causal nexus relates the alleged harm to the alleged infringement.*" *Apple II*, 695 F.3d at 1374 (emphasis added). Takeda has made no effort to satisfy this controlling legal standard.

While Takeda argues it would be irreparably harmed because it "anticipates losing" a substantial number of Colcrys® prescriptions to generic competition (Br. 17), this ignores the second irreparable-harm requirement. Takeda has offered no evidence of "a sufficiently strong causal nexus" to Hikma's induced infringement. This omission, alone, defeats the motion.

The Federal Circuit and this District have repeatedly emphasized this nexus requirement for showing irreparable harm in patent cases: "Sales lost to an infringing product cannot irreparably harm a patentee if consumers buy that product for reasons other than the patented feature." *Apple, Inc. v. Samsung Elecs. Co., Ltd.*, 678 F.3d 1314, 1324 (Fed. Cir. 2012) ("*Apple I*"); *accord Depuy Synthes Prods., LLC v. Globus Med., Inc.*, No. 11-652-LPS, 2013 WL 4509655, at *2 (D.

Del. Aug. 22, 2013) (emphasis added) (citation omitted); *Riverbed Tech., Inc. v. Silver Peak Sys., Inc.*, No. 11-484-RGA, 2014 WL 4695765, at *10 (D. Del. Sept. 12, 2014).

Here, the record shows that—at least 95% of the time—consumers buy colchicine product for reasons other than the patented methods. Even if Takeda somehow could manage to prove that Hikma will induce physicians to prescribe the drug for the roughly 5% market segment covered by Takeda's patents, such infringement would be *de minimis*—harm plainly compensated with a reasonable-royalty damages award. As in *Riverbed*, any such "nexus here is simply too tenuous" to justify the "drastic and extraordinary remedy" of injunctive relief. 2014 WL 4695765, at *13. This is because *de minimis* infringement cannot, as a matter of law, support a showing of irreparable harm. *See Roper Corp. v. Litton Sys., Inc.*, 757 F.2d 1266, 1273 & n.6 (Fed. Cir. 1985) (affirming denial of a preliminary injunction where the defendant made a strong showing of non-infringement and, at most, *de minimus* infringement).

Regardless, Takeda cannot even show that competitive "harm" caused by *non-infringing* competition would be irreparable. A mere showing that generic competition could affect the sales or market share of Takeda's branded product is not sufficient to establish irreparable harm. *See Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1347-48 (Fed. Cir. 2006). If it were, "'reliance on possible market share loss would apply in every patent case where the patentee practices the invention,' and is not justification for the extraordinary relief of a preliminary injunction." *Digene Corp. v. Ventana Med. Sys., Inc.*, 484 F. Supp. 2d 274, 285 (D. Del. 2007).

III. The Balance Of Hardships Cuts Against A Preliminary Injunction.

A preliminary injunction would cause significant hardship to Hikma. It spent years working with the FDA, and devoted [redacted] in drug development, to launch its generic colchicine product *solely* for a non-infringing use. (Gavaris Decl. ¶ 14-16.) Hikma's business focuses on selling generic drugs. (*See Id.* at ¶ 1; Todd Decl. ¶ 66.)[redacted]

[redacted] Extending the TRO would cause [redacted] [redacted] (*Id.*; *see also* Todd Decl. ¶ 69-71.)

Indeed, the TRO already has caused competitive harm. After approval (and before the TRO) Hikma *lawfully* launched a generic colchicine product that is *not* a duplicate of Colcrys® and is *not* automatically substituted at pharmacies. (Saseen Decl. ¶ 17.) [redacted]

Additionally, the Court's TRO has inverted the status quo—[redacted] if the Court were to find that an injunction should not have issued. Indeed, [redacted] would have a significantly chilling effect upon generic competition, because [redacted] ultimately harming consumers.

IV. Denying Injunctive Relief Would Further The Public Interest.

Lastly, each day an injunction bars generic competition, patients are harmed. As the American College of Rheumatology told FDA, "the price of [colchicine] has increased from approximately 10 cents per tablet to five dollars per tablet. This increase will put the drug out-of-reach of many patients." (Gavaris Decl. ¶ 11, Ex. B; ; Gattuso Ex. G at 1 (due to Takeda's monopoly, "the retail price … skyrocketed to more than $5 [per pill]" from "just pennies a tablet"); *Id.* at 2 (patients "can't afford Colcrys"). There is no public interest in allowing Takeda to block competition from Hikma's AG where, as here, at least 95% of the market is non-patented.

V. A Bond Under Rule 65(c) Must Be Posted With Any Preliminary Injunction.

Upon issuance of any further injunctive relief, Rule 65(c) requires that Takeda post additional security, separate from the TRO bond, for the potential harm Hickma would experience should Defendants prevail at trial. *See Howmedica Osteonics v. Zimmer Inc.*, 461 Fed. Appx. 192, 198 (3d Cir. 2012). As detailed in the Snail Declaration, based on Takeda's own assumptions, if Hikma were enjoined for a 12-month period through trial,[4] but ultimately prevailed, it can reasonably expect to suffer damages in the range of [redacted].

CONCLUSION

For the foregoing reasons, Takeda's motion for preliminary injunction should be denied.

[4] Should the Court order trial on a different schedule, Defendants can provide updated calculations.

PROCTOR HEYMAN LLP

/s/ Dominick T. Gattuso
Dominick T. Gattuso
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@proctorheyman.com

Attorneys for Defendants West-Ward Pharmaceutical Corporation, Hikma Americas Inc. and Hikma Pharmaceuticals PLC

OF COUNSEL:

WINSTON & STRAWN LLP
James F. Hurst
Samuel S. Park
Sharick Naqi
Lesley M. Hamming
35 W. Wacker Drive
Chicago, Illinois 60601-9703
(312) 558-5600
jhurst@winston.com
spark@winston.com
snaqi@winston.com
lhamming@winston.com

WINSTON & STRAWN LLP
Charles B. Klein
Steffen N. Johnson
John K. Hsu
1700 K Street, N.W.
Washington, DC 20006
(202) 282-5000
cklein@winston.com
sjohnson@winston.com

GOODWIN PROCTER LLP
Elaine H. Blais
John T. Bennett
53 State Street
Boston, MA 02109
Tel.: (617) 570-1000
Fax: (617) 523-1231
eblais@goodwinprocter.com
JBennett@goodwinprocter.com

GOODWIN PROCTER LLP
Elizabeth J. Holland
The New York Times Building
620 Eighth Avenue
New York, NY 10018
Tel.: (212) 813-8800
Fax: (212) 355-3333
EHolland@goodwinprocter.com